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Historical and Modern Epidemiological Studies on Populations Exposed to N-Substituted Aryl Compounds

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The historical exposures to aromatic amines of various occupational groups are briefly reviewed. Modern studies indicate that other occupational groups might have risks worth investigating; these include machinists and workers in the chemical industry. Details of a recent investigation into the exposure of dye workers are given which indicate a lowered risk in recent years since the introduction of safety measures. Nonoccupational exposures to the aromatic amines are also discussed. They include cigarette smoking and phenacetin abuse, the former being a potent causal agent in bladder cancer.

Introduction

The history of human exposure to aromatic amines probably starts with the observations of Rehn (*1*) of German aniline dye workers. He observed four cases of bladder cancer out of a probable total of 500 workers employed in the plant at that time. These observations sparked off a huge controversy over the next 30 years which had several significant consequences. The attempts to understand what hazards existed in industrial situations led to the development of some of the techniques of modern epidemiology, in particular the cohort or follow-up study. The observation not only drew attention to bladder disease at that time, it ensured that bladder cancer would be studied almost to the exclusion of all other diseases in industrial situations. This is almost as true today as 40 years ago, in part due to the more recent use of the case-control approach. Finally, and most importantly, it led to the development of laboratory analyses which demonstrated the biochemistry of causal association and which, along with the epidemiological results led to the demise of those industrialists who claimed the associations were fortuitous.

The early history of industrial aromatic amine exposure was one of claim and counterclaim: first, about the nature of the excess numbers of bladder cancer cases; second, about which chemicals were implicated; and finally about the natural history of "industrial" bladder cancer as contrasted with other types. The controversy over the existence of excessive bladder cancer cases was finally resolved by Case et al. (*2, 3*), who also contributed to the identification of some of the carcinogenic chemicals. The assertions that "industrial" bladder cancer is a more aggressive disease has yet to be fully resolved, although some evidence for this is now forthcoming (*4*).

The Dye Manufacturing Industry

Case (*5, 6*) computed the number of male bladder cancer deaths between 1921 and 1951 among a group of workers from dye manufacturing companies and contrasted this with male deaths due to bladder cancer from the totality of England and Wales. He expected, on this basis, four bladder cancer deaths and found 127 in the dye industry. In addition the records were such that it was possible to estimate the exposure to several suspect substances. They showed that 25% of all the men exposed to aromatic amines, including benzidine and 2-naphthylamine, developed bladder cancer. Those men only exposed to benzidine in fact had fewer tumors (15%) and those only exposed to 2-naphthylamine had more (50%). The few individuals who distilled 2-naphthylamine all died of bladder cancer.

Case (*6*) also showed that the deaths occurred earlier among dye workers than the general population, having excessive occurrences under the age of

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65. He also computed a median latent period from first exposure of eighteen years; the range, however, is between 5 and 63 years (*7*). Case estimated in 1952 that of the workmen exposed to aromatic amines between 1921 and 1952, another 243 cases would accrue in the U.K., even if all exposure were withdrawn at that time due to the latency of the disease. Table 1 shows the distribution of this risk. Case's estimates have unfortunately proved, by 1982, to be too low. Work by Scott (*8*) indicated that 1-naphthylamine was also a suspect chemical, although this is possibly erroneous due to mixed exposures with 2-naphthylamine.

Rubber and Cable-Making Industries

Case and Hosker (*9*) investigated the rubber industry in the early 1950s and found an excessive number of bladder cancer deaths. This resulted in a standardized mortality ratio (SMR) of 164 for bladder cancer. Since then exhaustive studies have been undertaken which indicate that the risk of bladder cancer in these industries is largely historical although still high in a few occupational subgroups due, once more, to the long latent period. In addition to bladder cancer, both lung and stomach cancers were excessively high in rubber industry workers.

The bladder cancer risk has been ascribed to the contamination of the various rubber antioxidants by naphthylamine isomers. The picture is more complex than that, however, due to the numerous other chemicals, such as reinforcing agents and organic accelerators, added to rubber in its manufacture.

In addition, due to the differences in industrial practices in the United States, where 4-aminobiphenyl was used, U.S. workers had a lower risk of bladder cancer than British workers. As in the U.K., the U.S. risks now seem historical, and once more excesses of other tumors have been observed among exposed workers, including lung cancers, stomach cancers and leukemias. The significance of these observations has always been in doubt due to the wide variety of chemicals used in the rubber industry and the weak statistical associations. The same complex picture is seen in the rubber cable-making industry although, once more, an excess of bladder tumors did once exist (*10*).

Gas Workers

Workers engaged in the production of coal gas were shown by Doll et al. (*11*) to have slight excess of bladder cancer and larger excesses of lung cancer and of chronic respiratory diseases such as chronic bronchitis. As aromatic amines constitute only a small part of the inhaled gases in such establishments, the significance of these results remains in some doubt. In addition, due to natural gas, this industry has disappeared from most European countries, and no work has been undertaken on this topic recently.

The Regulations

The studies referred to so far represent the classical work on aromatic amine exposure to industrial groups. The controlling regulations used in the U.K., the Carcinogenic Substances Regulations, are based upon them as well as the current clinical suppositions about bladder cancer etiology existing at that time. The controlled or prohibited substances are: α-naphthylamine, β-naphthylamine, dichlorobenzidine, 4-aminodiphenyl, auramine and magenta, *o*-dianisidine and *o*-tolidine. These regulations are still current in the U.K. more or less in their original form. In addition there are a group of occupations "recognized" as hazardous for compensation purposed in the U.K. These are: the chemical dye manufacturing industry and other branches of the industry handling the recognized substances, gas workers, laboratory workers, manufacture of rubber-coated cables, paint and pigment manufacturers, rodent controllers, rubber manufacturers and textile printers. Some groups, such as the rat catchers, have never been shown to be at risk; their inclusion is due to their use of α-naphtholthiourea (ANTU).

Naphthylamine manufacture ceased by 1953 in the U.K. and benzidine production disappeared by 1962. These chemicals are made in other parts of the world in a variety of plants—some automated without human exposure and some, sadly—in the

Table 1. Bladder tumors in chemical workers: estimated risks in 1952 of 2446 men at risk.

Exposure	Cases found	New cases expected	Total
Benzidine	34	24	58
1-Naphthylamine	19	51	70
2-Naphthylamine	55	38	93
Mixed exposure	135	130	265
Total	243	243	486

developing world—with old-fashioned techniques leading to excessive human exposure.

Modern Industrial Studies

Very few follow-up studies have added substantially to our knowledge of the processes or hazards to humans of aromatic amine exposure since the 1960s. One such study, however, on a modern German auramine plant has indicated little risk to the work force there (*12*), contrary to the earlier work of Case (*3*).

Most studies have addressed the question: are aromatic amines found in other industrial or nonindustrial environmental situations, and do they cause an excessive number of bladder cancers as a result? Table 2 summarizes the main conclusions from a variety of these studies. Table 2 ignores the traditional occupations. These studies present a confusing array of results, which contain some explicable occupations such as the kimono painters and leatherworkers who used benzidine-based dyes. In addition, some textile workers, paint manufacturers and hairdressers could also have contact with dangerous coloring agents. It is also conceivable that metal workers might have contact with aromatic amines from fluxes or as partly combusted substances from furnaces, although no conclusive hygiene work has been undertaken on this topic among these groups. Other groups with excessive numbers of bladder cancers, including, sailors, coal miners and clerical workers, are difficult to assess as to their possible exposure to occupational aromatic amines. Possibly other factors of a nonoccupational nature are involved in these instances or these are fortuitous observations thrown up by the multiple comparisons made by the case-control analysis techniques. More credance might be accorded these observations if other studies confirmed the associations.

Table 2. Summary of new occupational risks resulting from descriptive and case-control study design.

Occupation	Reference
Leatherworkers	(*13-15*)
Japanese kimono painters	(*16*)
Dye users in textiles	(*14, 17*)
Hairdressers/barbers	(*14, 18*)
Metal workers/machinists	(*14, 18*)
Coal miners	(*14*)
Paint manufacturers, painters and decorators and spray shop workers	(*14, 15*)
Textile industry (females)	(*14, 17*)
Sailors	(*18*)
Tin and coppersmiths	(*18*)
Civil engineers and other types	(*17, 18*)
Plumbers	(*18, 19*)
Aluminum reduction workers	(*20*)
Carpenters	(*18*)
Medical workers including nurses	(*17, 21*)
Tailors and tailor's pressers	(*17*)
Cooks, kitchen hands and food industry workers	(*15, 21*)
Clerical workers	(*15*)
Photographic industry workers	(*21*)
Stone masons	(*19*)

West Yorkshire Bladder Cancer Studies

The author has recently completed a case-control study of occupational exposure and bladder cancer in West Yorkshire. Analyses so far incorporate results on 1259 cases and 1981 controls from specific areas in Yorkshire. Table 3 gives overall results for a few occupational groups. Clerical workers have a low but statistically significant risk, as do cooks, machinists and woodworkers. Machinists are a large group of workers in this area, and although the risk is quite low, the population attributable risk will be high. Further analyses are underway among machinists. There is evidence that some of the mineral oils used by the lathe operators contains aromatic amines as emulsifiers and corrosion inhibitors.

Table 3. West Yorkshire case-control study: analysis of 1259 cases

Occupational group	Number of cases	Risk ratio[a]	95% Confidence limits
Clerical workers	194	1.4	1.2-1.7
Cooks and bakers	37	1.8	1.1-2.9
Chemical workers	115	2.2	1.7-2.9
Dye users in woolen trade	35	(0.9)	0.6-1.4
Machinists	101	1.4	1.1-1.9
Hairdressers	12	(0.6)	0.3-1.2
Tanners	4	(6.3)	0.9-42.8
Other leatherworkers	19	(1.0)	0.6-1.8
Woodworkers	67	1.5	1.0-2.0

[a]Results given in parentheses are insignificant at 5%.

Table 4. West Yorkshire case-control study: dye manufacturing workers.

	N	Risk Ratio[a]	95% Confidence limits
All chemical workers	115	2.2	1.7-2.9
Dye manufacturing workers	82	3.4	2.3-4.9
Other chemical workers	33	(1.3)	0.8-2.0

[a]Results given in parentheses are insignificant at 5%.

Table 5. Dye manufacturing process workers: risks by period of first exposure (Mantel-extension test).[a]

Time of first exposure	SRR
Before 1940	4.4
1940-1951	3.3
1952-1960	1.4
After 1960	1.3

[a]Chi (M-H) = 6.8, p = <0.01.

Table 6. Dye manufacturing process workers: length of exposure (Mantel-extension test).[a]

Duration of exposure, years	SRR
< 5	1.7
5-9	1.7
10-19	4.3
20-29	7.1
> 30	8.0

[a]Chi (M-H) = 7.3, p = <0.01.

West Yorkshire also contains a large number of aromatic amine-exposed dye manufacturing process workers. Results on these groups are given in Table 4 and show that the risk of bladder cancer is still high, despite controlling measures dating back 30 years. However, the risk is largely historical, as shown in Table 5, which indicates that dye workers subdivided by year of starting work, have a greatly reduced (and statistically insignificant) risk of developing bladder cancer when first exposed after 1952. Table 6 indicates that the length of exposure to these substances is also important: exposure of less than 10 years results in a much smaller risk, even prior to 1940 when precautionary working practices were nonexistent. Undoubtedly the cases presented in recent years are a somewhat biased group, because those heavily exposed for short periods could have died of the disease prior to the start of our study and other cases could arise in the future having been exposed many years previously.

These data need careful analysis prior to full presentation, but two further studies have resulted: a detailed analysis of those exposed to machine oils and a new cohort study in the chemical industry in a plant manufacturing 4,4′-methylenebis(2-chloraniline) (MBOCA), used as a hardener for plastics. This plant has had 13 new cases of bladder cancer in the last few years—far more than that which might be expected. It is possible that this substance, or its manufacture, is carcinogenic to men. Some work has been recently completed on anthraquinone exposure in a factory in Scotland; the results indicate no excessive risk to the work force. With these few exceptions many aromatic amines have had little epidemiological attentions. Table 7 summarizes what human evidence of aromatic amine contact that is available and allows some conclusions to be made. Table 8 lists some of those chemicals for which data are completely absent.

Nonoccupational Exposure to Aromatic Amines

Cigarette smoke contains aromatic amines along with many other compounds, and, although it is not possible to be absolutely confident of the chemical nature of the association, there is no doubt that cigarette smoking produces an excess of bladder tumors. Table 9 is taken from Wynder (*29*) and gives the risk for males for broad categories of smokers and nonsmokers. Recent results from Yorkshire are included. The studies vary in both case and control ascertainment, as well as conduct and study analysis. It is difficult to summarize these results except to say moderate to heavy cigarette consumption doubles the risk of bladder cancer. Most results from females show a slightly lower risk than the comparable male result.

Phenacetin ingestion over long periods or in quantities over 1 g/day for at least a year (*30*) leads to renal papillary necrosis and to tumors of the urothelium of the renal pelvis. Over 100 cases have been reported, largely from Scandenavia, where such abuse was not uncommon. Transitional cell tumors of the renal pelvis are excessively rare in the U.K., however. In a series of all urothelial tumors in Yorkshire, 2.4% proved to be arising in the renal pelvis. One out of 15 of these cases proved to have been a chronic phenacetin taker. This suggests the problem is not a serious one in the U.K., although tumors still occur due to this reason.

It has been recently suggested, however, that tumors lower down the renal tract, in the ureter and bladder, may also result from phenacetin abuse. A

Table 7. Evidence for human carcinogenicity of aromatic amines: some human data available.

Compound	Data	References and comments
Aniline	No evidence	(2, 3)
o-Toluidine	Slight evidence	Three cases of cancer of bladder
p-Chloro-*o*-toluidine	No evidence	(22)
2,5-Diaminotoluene	Slight evidence	Two cases of aplastic anemia
Anthranilic acid	No evidence	
4-Biphenylamine	Good evidence	(23, 24)
4-Nitrobiphenyl	Slight evidence but mixed with other amines	
Benzidine	Good evidence	(25)
3,3′-Dichlorobenzidine	Slight evidence but mixed with other amines	
3,3′-Dimethoxybenzidine	Slight evidence but mixed with other amines	
4,4′-Methylenebis(2-chloraniline)	Slight evidence	
1-Naphthylamine	Slight evidence but mixed with other amines	(2, 3)
2-Naphthylamine	Good evidence	(26)
N,*N*-Bis(2-chloroethyl)-naphthylamine	Good evidence	(27)
N-Phenyl-2-naphthylamine	Some evidence	(28)
Auramine	Slight evidence	(3)
	No evidence	(12)
Magenta	Slight evidence but mixed with other amines	(3)

Table 8. Human carcinogenicity of aromatic amines: no data available.

Compound
5-Nitro-*o*-toluidine
3-Chloro-*p*-toluidine
p-Phenylenediamine
m-Phenylenediamine
4-Chloro-*m*-phenylenediamine
4-Chloro-*o*-phenylenediamine
2,4-Xylidine
2,5-Xylidine
2,4-Diaminotoluene
1,2-Diamino-4-nitrobenzene
1,4-Diamino-2-nitrobenzene
2,4-Dinitrotoluene
4-Amino-2-nitrophenol
o-Anisidine
5-Nitro-*o*-anisidine
p-Anisidine
2,4-Diaminoanisole
m-Cresidine
p-Cresidine
3-Amino-2-ethoxyacetanilide
2,4′-Biphenyldiamine
N,*N*′-Diacetylbenzidine
3,3′-Dimethylbenzidine
4,4′-Thiodianiline
4,4′-Diaminodiphenyl ether
4,4′-Methylenedianiline
4,4′-Methylenebis(2-methylaniline)
4,4′-Bis(dimethylamino)benzophenone

Dutch study (*31*) gives a 4-fold excess risk in those who consumed this analgesic. If these data can be repeated elsewhere, this could prove to be an important cause of bladder cancer.

Chlornaphazine or *N*,*N*-bis(2-chlorethyl)-2-naphthylamine is a now defunct agent once used in the treatment of a variety of malignancies including Hodgkin's disease, some leukemias, and polycythemia rubra versa. Videbaek (*32*) and Thiede et al. (*33*) reported excessive numbers of bladder cancers arising in these patients, and there is no doubt this was due to the administration of this particular drug (*27*).

Table 9. Cigarette smoking and bladder cancer in males.

Country	Years	Risk Ratio
U.S.	1957-60	3.5
U.S.	1951-61	7.3
Poland	1958-64	2.7
U.S.	1958-64	1.4
U.S.	1967-68	1.9
U.S.	1965-71	1.6
Egypt	1966-71	1.7
U.S.	1969-74	3.0
Canada	1972-73	6.4
Austria	1972-75	1.6
U.K. (Yorkshire)	1977-81	1.6

There may well be many other aspects of human nonoccupational exposure to aromatic amines through a wide variety of agencies: food colorants, or oils, for example. There are few practical situations where epidemiological studies would result in useful and clear answers. One exception to this has recently come to light in England, and it helps to illustrate that a careful watch of our environment is still required.

The example concerns coarse fishermen—a very popular sport in the U.K. with over 4 million regular participants. Anecdotal accounts led to a chemist investigating the activities of these men, only to find that they commonly used maggots of the blue-bottle flies as hooked and ground bait. This practice is innocuous, except the majority of keen fishermen stain their maggots. The stains used are: Chrysoidine γ (2,4-diaminoazobenzene), Rhodamine, Auramine O, Methylene Blue and Bismark Brown. The most popular is the bronze-staining Chrysoidine or Basic Orange 2, whose active constituent is 1,2,4-triaminobenzene (*34*). These substances are used in powder form by fishermen and are readily available over the counter in England. The fishermen stain their fingers, put maggots in their mouths and have every opportunity to absorb these dyes. We are actively investigating the possibility that these fishermen might have excessive rates of bladder cancer. These observations could be of great significance, because industrially based epidemiological studies on azo dye workers can produce confused results due to mixed exposures, while fisherman have had much simpler and easily extractable exposures.

Conclusion

There is strong human evidence for the association of bladder and renal pelvis cancers with specific aromatic amines. There is weaker evidence that stomach and lung cancer are found in excess in those exposed to particular amines. In addition the effects of human exposure on a large range of compounds is unknown.

It should be remembered, however, that there is little or no evidence to incriminate some aromatic amines, auramine and aniline, for example. It is likely that many aromatic amines in their pure state present little or no hazard to humans, but this remains to be demonstrated when appropriate epidemiological situations arise.

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